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EXAMINER
DUNSTON, JENNIFER ANN

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,242	LIEW ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6,9,12 and 29-61* is/are pending in the application.

4a) Of the above claim(s) *3,6,9,12,29-33 and 53-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1636.

Receipt is acknowledged of an amendment, filed 5/3/2006, in which claims 1-2, 4-5, 7-9, 10-11 and 13-28 were canceled; claims 3, 6, 9, 12 and 29-36 were amended; and claims 37-61 were newly added. Currently, claims 3, 6, 9, 12 and 29-61 are pending.

Election/Restrictions

Applicant's election with traverse of Group II (formerly claims 13-28 and 34-36) and TNFAIP6 and TGFB1 as the combination of biomarkers in the reply filed on 3/29/2006 is acknowledged. Upon the amendment of the claims in the reply filed 5/3/2006, claims 3, 6, 9, 12 and 57-60 read on the invention of Group I, claims 34-52 read on the invention of Group II, and claims 29-36 and 53-56 read on the invention of Group III.

The traversal is on the ground(s) that examining all claims would not constitute an undue search burden on the Examiner. Further, the response asserts that a search of the product claims comprising Group I would necessarily be encompassed by a search of the method claims of Group II, which incorporate said product, and that the claims of Groups II and III are sufficiently related such that their searches would be significantly overlapping. This is not found persuasive because the inventions of Groups I-III are each separately classified. Furthermore, a separate search is required for the products of Group I and method of Group III. The search of the product is not coextensive with the search of the method of Group II, because the product of

Group I may be used in a method other than the method of Group II. Thus, a search of the product will not necessarily identify the claimed method. A separate search of the patent and non-patent literature would be required for the methods of Groups II and III in order to search the method steps not shared between each of the groups. For example, a search of the patent and non-patent literature for the step of determining a difference in the level of expression of a biomarker in a first sample from a patient prior to treatment as compared to a second sample after treatment would be required for the search of Group III and is not required for the search of Group II. Further, the search for the step of comparing the level of expression of RNA in a sample from a patient with the level of expression of the RNA in one or more control samples diagnosed with either moderate or marked osteoarthritis is not required for the search of Group III but is required for the search of Group II. Accordingly the searches of Groups I-III are not coextensive, and the additional searching required to search more than Group II would impose a serious search burden.

The response further traverses the restriction requirement within Group II. The response asserts that the restriction to one combination of gene should be a requirement for the election of species. This is not found persuasive because each combination of nucleotide sequences is a distinct invention. For example, the combination of A and B will not anticipate or render obvious the combination of C and D. However, if the elected combination of TNFAIP6 and TGFB1 is found allowable, Applicant may claim additional patentably indistinct combinations of markers comprising TNFAIP6 and TGFB1 pursuant to MPEP 803.04. The patentably indistinct combinations will then be fully examined.

The requirement is still deemed proper and is therefore made FINAL.

The response filed on 3/29/2006 requests rejoinder of the product claims of Group I and method claims of Group III if the method of Group II is found allowable. Applicant did not elect the product claims of Group I. Therefore, rejoinder of the patentably distinct inventions will not be offered. See pages 5-6 of the Office action mailed 9/29/2005 for an explanation of rejoinder practice.

Claims 3, 6, 9, 12, 29-33 and 53-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/29/2006.

Priority

A nonprovisional application claiming the benefit of a provisional application is not required to be copending with the provisional application. Abandonment of a provisional application for failure to pay the basic filing fee would indicate that the nonprovisional application could not claim the benefit of the provisional application because the basic filing fee was not paid within the time period set forth in 37 CFR 1.53(g) as required by 37 CFR 1.78(a)(4).

In the instant case, provisional application number 60/410,180 was <u>not</u> abandoned for failure to pay the basic filing fee.

Specification

It is suggested that the figures, which contain text concerning the differential expression of genes in osteoarthritis, be incorporated as TABLES into the specification. As figures, this data is not text searchable in the US patent databases. Putting the information into text-based tables would make the information more search-accessible to the public in the event this application issues as a patent.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Applicant must thoroughly review the specification and identify all embedded hyperlinks. For example, hyperlinks are found at page 59, line 9 and page 93, line 17.

The disclosure is objected to because of the following informalities: the word "from" is misspelled at page 97, line 16. Appropriate correction is required.

Claim Objections

Claims 34-36 are objected to because of the following informalities: the claims depend from claims withdrawn as being drawn to a non-elected invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35, 36, 38, 42, 46 and 50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 21 and 25 of copending Application No. 10/809,675 (hereinafter the '675 application).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 38, 42, 46 and 50 are drawn to a method of diagnosing mild, severe, moderate or marked osteoarthritis, respectively, comprising the steps of (i) determining the level of expression of RNA corresponding to one or more biomarkers in a sample of the individual to be diagnosed, and comparing the level of expression in the sample with the level of expression of RNA corresponding to said biomarkers in one or

more control samples wherein the control samples are from individuals that have been diagnosed with a different stage of osteoarthritis. Conflicting claim 13 is narrower in scope in that the sample is limited to blood. Although conflicting claim 13 does not specifically recite each of the stages of osteoarthritis within the claim, the method encompasses the diagnosis of mild, moderate, marked and severe osteoarthritis, as these are the stages of osteoarthritis defined by the specification of the '675 application. Thus, instant claims 38, 42, 46 and 50 are anticipated by conflicting claim 13. Further, Instant claims 35 and 36 are anticipated by conflicting claims 25 and 21, respectively.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37, 38, 41, 42, 45, 46, 49 and 50 are vague and indefinite in that the metes and bounds of the phrase "RNA corresponding to" are unclear. It is not clear what it means for an RNA transcript to correspond to a biomarker. The specification does not define the correspondence, and it is unclear if the term is meant to encompass only the expression of the human gene recited in the figures of the specification or if the term is meant to encompass the

expression of genes that are similar to the human gene in other animals and also in humans, etc. Accordingly the metes and bounds of the term are unclear. It would be remedial to amend the claim language to clearly indicate what RNA is being measured in the claimed methods.

Claims 34-36, 39, 40, 43, 44, 47, 48, 51 and 52 depend from claims 37, 38, 41, 42, 45, 46, 49 and 50 and thus are indefinite for the same reasons as applied to claims 37, 38, 41, 42, 45, 46, 49 and 50.

Claims 39, 43, 47 and 51 are vague and indefinite in that the metes and bounds of the phrase "one or more biomarkers are selected from those identified in Figures 1-7" are unclear. The term is unclear in that the referenced figures refer to SEQ ID NOS, gene descriptions, gene name, Gene Accession Numbers, UniGene numbers, etc. Therefore, it is not clear if the claims intend to be requiring the assay of any gene which meets the gene description or any gene which has the name recited in the "gene name" column of the figure, including any potential variants or alternate splice sites of the gene. The claims should be clarified as to what precisely is being determined.

Claims 34-36 depend from claims 39, 43, 47 and 51 and thus are indefinite for the same reasons as applied to claims 39, 43, 47 and 51.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claims 37-40 are specifically drawn to a method of diagnosing mild osteoarthritis in an individual. Claims 45-48 are specifically drawn to a method of diagnosing moderate osteoarthritis in an individual. Claims 49-52 are specifically drawn to a method of diagnosing marked osteoarthritis in an individual. Claims 41-44 are specifically drawn to a method of diagnosing severe osteoarthritis in an individual.

Claims 38, 42, 46 and 50 comprise the method step of "determining the level of expression of RNA corresponding to one or more biomarkers of said individual." Claims 39, 43, 47 and 51 further limit the biomarkers to one or more biomarkers selected from the group identified in Figures 1-7. Claims 37, 40, 41, 44, 45, 48, 49 and 52 are drawn to determining the level of expression of RNA corresponding to biomarkers TNFAIP6 and TGFB1, the elected invention. To diagnose the individual with either mild, moderate, marked or severe osteoarthritis, the expression of the biomarkers is compared to the expression of the biomarkers in one or more control samples, where said control samples are individuals that have been diagnosed with osteoarthritis of known severity.

Claims 34-36 limit the sample to human cartilage, the biomarker to one that is immobilized on a microarray, and the determination of the level of expression by hybridization or microarray, respectively.

The nature of the invention is complex in that the expression of the biomarkers recited in the claims must be able to distinguish between mild, moderate, marked and severe osteoarthritis when gene expression is compared between the test individual and one control individual with osteoarthritis of known severity, classified according to the Marshall scoring system disclosed in the instant specification. The practice of the claimed invention for the diagnosis or staging of osteoarthritis requires the knowledge of gene(s) that are differentially expressed between "normal", mild osteoarthritis, moderate osteoarthritis, marked osteoarthritis, and severe osteoarthritis. Furthermore, the alterations in gene expression between the different classes must be consistent enough within each class and between each class such that a diagnostic test of sufficient specificity and sensitivity can be performed. In other words, the gene expression patterns tested in the claimed methods must allow one to draw a reliable conclusion regarding the presence/absence of osteoarthritis and the severity of osteoarthritis.

Breadth of the claims: The claims are very broad in that they encompass the use of any RNA as a biomarker diagnostic of mild, moderate, marked or severe osteoarthritis. With respect to the choice of biomarker, the claims encompass the use of the same biomarkers for the diagnosis of osteoarthritis of differing severity. The language used to define the detected RNA is also broad in nature, requiring only that the level of RNA "corresponding" to the disclosed biomarkers be determined. Accordingly, the claims encompass the detection of RNA expression from genes that are homologs, variants, and the like of the biomarkers. Further, the claims are

broad in that they encompass the detection of any difference in gene expression such as up- or down-regulation of the RNA expression for a biomarker. Moreover, the claims encompass the use of any sample (e.g. blood, synovial fluid, cartilage) from any species of organism, as the claims are sufficiently broad so as to include the diagnosis of osteoarthritis in any species that would have transcripts that hybridize or "correspond" to the biomarkers.

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches that "diagnosis" refers to a process of determining if an individual is afflicted with a disease or ailment (page 14, lines 27-28). The specification does not provide a single working example where the claimed method is actually practiced for the diagnosis or staging of OA in a patient, human or otherwise. The specification provides an experimental section with "examples," but these are not examples of the instantly claimed method being used.

The specification asserts that Figures 1-7 contain lists of stage-specific genes, whose level of expression is indicative of the existence of some degree of mild, moderate, marked or severe osteoarthritis when compared with the level of expression of the same one or more genes in a normal individual (e.g. page 36, lines 18-22; page 85, lines 14-22). It is noted that the claimed methods do not require the comparison of the expression of the biomarker(s) of Table 1-7 in a test subject to the level of gene expression in a normal individual.

The examples of the specification teach the isolation of RNA from normal human cartilage and cartilage samples from areas of mild, moderate, marked or severe cartilage degeneration obtained during either arthroscopic knee surgery or total knee replacement (e.g.

pages 91-92). The specification teaches that the RNA was made into a cDNA library, from which cDNA clones (ESTs) were obtained and sequenced (e.g. page 92). The specification does not teach the number of individuals from which each cDNA library was made. The EST sequences obtained from this analysis were used to make a microarray of genes expressed in normal and diseased articular cartilage. This array appears to be referred to as the ChondroChip array in the remainder of the specification.

The examples of the specification teach that RNA samples isolated from normal or OA articular cartilage can be labeled and hybridized to the ChondroChip or Affymetrix U133A Array (e.g. pages 94-96).

Example 5 asserts that biomarkers (nucleic acids) specific for mild OA or severe OA were detected utilizing the ChondroChip. The specification states that sample RNA from either normal, mild or severe OA cartilage was labeled and hybridized to the ChondroChip with subsequent analysis identifying differences in gene expression greater than 2-fold when compared to either the intensity from the normal cartilage or any other stage specific cartilage (page 97). The specification does not teach the number of individuals analyzed for each sample class. It is unclear whether a single sample was used for each class, multiple samples were pooled for each class, or multiple samples were individually tested for each class. The nature of the comparisons is wholly unclear. For example, the specification does not teach whether each class of OA was directly compared to normal cartilage in the hybridization assay. The specification asserts that Figures 1-4 provide those genes identified as unique to either mild or severe OA. Thus, tables 1-4 do not provide any information with regard to moderate or marked osteoarthritis. Because moderate and marked OA samples were not included in this study, it is

impossible to determine whether genes that differentiate between mild and severe OA will also differentiate between mild, moderate, marked and severe OA.

Example 6 asserts that biomarkers specific for mild OA, marked OA, moderate OA and severe OA were determined. The specification teaches the hybridization of samples of RNA from normal, mild OA, moderate OA, marked OA and severe OA to the ChondroChip and Affymetrix U133A Array. The specification states that the following pairwise comparisons were made: mild/normal, moderate/normal, marked/normal and severe/normal. Using statistical tests and a p-value cutoff of 0.05, genes "associated" with OA were identified and are presented in Figures 6 and 7. These genes appear to be genes up- or down-regulated in OA, which are not affected by age, gender, hybridization date, and slide batch. This suggests that multiple samples were tested on multiple days; however, the specifics are not provided in the instant specification.

The specification characterizes the figures of the instant specification in the following manner:

Figure 1: ESTs down-regulated in cartilage isolated from patients having mild osteoarthritis, but which are not down-regulated in patients having severe osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 2: ESTs down-regulated in cartilage from patients having severe osteoarthritis, but which are not down-regulated in patients having mild osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 3: ESTs up-regulated in cartilage isolated from patients having mild osteoarthritis, but which are not up-regulated in patients having severe osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 4: ESTs up-regulated in cartilage from patients having severe osteoarthritis, but which are not up-regulated in patients having mild osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 5: ESTs up regulated in patients having mild osteoarthritis when compared to cartilage isolated from normal individuals.

Figure 6: ESTs which have been identified as being OA stage-specific markers for (a) mild OA only, (b) moderate OA only, (c) marked OA only, and (d) severe OA only in OA ChondroChip microarray analysis.

Figure 7: ESTs which have been identified as being OA stage-specific markers for (a) mild OA only, and (b) severe OA only in OA cartilage as compared to cartilage isolated from normal individuals, when the Affymetrix U133A Array is used for the analysis.

Figures 1-5 do not provide any information regarding the status of the genes or biomarkers in moderate or marked OA. Accordingly, one cannot definitively classify the stage of OA in a test individual as being mild, moderate, marked or severe based upon the data presented in Figures 1-5.

While the specification asserts that Figures 6 and 7 present data for biomarkers that are specific to one stage of OA only, the same biomarker can be found in more than one category. For example, TGFB1 is found in Figure 6b (moderate OA only, pp. 61 and 62) and Figure 7a (mild OA only, p. 753), and TNFAIP6 is found in Figure 6c (marked OA only, p. 238) and Figure 7a (mild OA only, pp. 683 and 698). Therefore, the genes listed in tables 6(a-d) and 7(a-b) are not specific to one class of OA. If one were to test an individual for the expression of TGFB1 and TNFAIP6 in articular cartilage and compare that result to an individual diagnosed

with any class of OA, one would not be able to determine if the test individual has marked OA or mild OA). Furthermore, the specification does not teach the direction of expression. Perhaps, TNFAIP6 is up regulated in marked OA and down regulated in mild OA. However, the specification does not specifically teach the direction of gene expression relative to the normal control.

The specification does not teach the actual diagnosis of any individual using the claimed method. Further, the specification does not teach the specificity or sensitivity of a diagnostic test using any combination of biomarkers, including the combination of TNFAIP6 and TGFB1.

Predictability and state of the art: The prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph [0156]). Shalon et al teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph [0158]). Post filing art, Kroese et al (Genetics in Medicine, Vol. 6, pages. 475-480, 2004) teach genetic tests are heterogeneous in nature and the exact characteristics of a

particular genetic test to be evaluated must be tightly defined. Kroese et al teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (e.g. page 476, 2nd column, last paragraph). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g. page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g. page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, Vol. 18, page 20, 2004) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (e.g. page 3, 2nd paragraph).

With regard to gene expression testing to diagnose osteoarthritis, Marshall et al (Osteoarthritis and cartilage, Vol. 13, pages 861-871, 2005) teach that the level and direction of gene expression for a particular gene in a test sample and control may vary depending upon

whether the RNA used to assess the level of expression is obtained from blood or cartilage (e.g. page 868, paragraph bridging columns). Marshall et al specifically teach that TNFAIP6 has been shown to be up regulated in pre-inflamed joints and in OA cartilage, but is down regulated in early OA blood samples (e.g. page 868, paragraph bridging columns). Further, Marshall et al teach that extensive statistical analysis of numerous training and test samples must be done to determine the specificity, sensitivity and accuracy of an OA diagnostic test based upon gene expression assays (e.g. page 865, right column, 2nd full paragraph; page 869, left column; Table V).

The use of TGFB1 in the specific diagnosis of mild, moderate, marked or severe osteoarthritis would be unpredictable. The instant specification teaches that osteophytes are not observed in mild OA but are present in moderate and severe OA (e.g. pages 3-4). Thus, osteophytes are a feature of moderate, marked and severe OA. Uchino et al (Clinical Orthopaedics and Related Research, Vol. 377, pages 119-125, 2000) teach that TGFB1 is expressed in osteophytes and in OA articular cartilage (e.g. Table 2). Thus, it would be unpredictable to use TGFB1 alone or in combination with TNFAIP6 to diagnose a specific class of OA.

Amount of experimentation necessary: Given the lack of guidance in the specification and prior art with regard to using gene expression to diagnose mild, moderate, marked or severe osteoarthritis, the quantity of experimentation in this area is very large. Due to the lack of detail provided in the specification with respect to the direction of expression of the genes in Tables 6 and 7, and lack of statistical analysis with respect to the predictive value of any combination of

genes from Tables 1-7, one would have required a large amount of experimentation to carry out the claimed invention.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 34-52 are not considered to be enabled by the instant specification.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER